Best of the 2009 AUA Annual Meeting

Highlights From the 2009 Annual Meeting of the American Urological Association, April 25-30, 2009, Chicago, IL

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Almost 2300 posters, abstracts, and videos were presented at the 2009 annual meeting of the American Urological Association (AUA), held this year in Chicago, Illinois, from April 25 through 30. The editors of *Reviews in Urology* have culled the enormous volume of information from this premier source and present here the findings most relevant to the practicing urologist.

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Prostate Cancer

Tumor Markers

Prostate markers once again were a major topic at the 2009 AUA meeting. The recent publications in the *New England Journal of Medicine* of the European Randomized Study of Screening for Prostate Cancer (ERSPC) and Prostate, Lung, Colon and Ovarian (PLCO) screening trials—with apparently opposite results (the former showing a survival advantage, the latter none)—gave increased impetus to the need for novel markers for this most ubiquitous of male malignancies. The appropriate cutoff for serum prostate-specific antigen (PSA) level as an indication for biopsy remains ill defined.

The Prostate Cancer Prevention Trial (PCPT) clearly demonstrated a large number of men with cancer with serum PSA levels less than 4.0 ng/mL. Black and colleagues[1] looked at the intervention arm of the PLCO trial; 34,097 men were included in their review. The decision for biopsy in this trial was made by the subject's physician and was not protocol driven. Among 2547 men diagnosed with prostate cancer, 1455 had a PSA lower than 4.0 ng/mL. Cancer diagnoses reflected the level of PSA. Whereas only 0.3% of men with serum PSA levels less than 0.5 ng/mL had cancer, 67.1% of those whose PSA was higher than 10.0 ng/mL were positive. Of note, 24.2% of men with PSA in the range of 3.0 to 4.0 ng/mL had cancer. Despite the fact that the authors observed substantially equivalent frequency of Gleason 7 or greater cancer at all serum PSA levels (28.1% vs 24.8% for serum PSA ranges 3.0-4.0 and 4.0-7.0, respectively), they concluded that a cutoff of 4.0 ng/mL remains appropriate. As noted, this trial failed to show a survival benefit for screening. Perhaps this in part is because too few cancers were detected at a time

when intervention would have been beneficial—a factor that would have been testable if protocol-driven biopsy was used.

The effect of subclinical prostatitis on serum PSA levels was investigated by Griffin and colleagues.[2] One hundred and seventy-nine consecutive men undergoing prostatic evaluation with serum PSA levels higher than 2.5 ng/mL and no evidence of prostatitis on urinalysis or culture underwent transrectal ultrasound-guided needle biopsy (TRUS Bx); 127 had a 2-week course of empirical antibiotics followed by repeat PSA testing. Men who responded with a higher than 25% decrease in serum PSA were offered biopsy deferral. Biopsy was positive in 47% of nonresponders, 36% of partial responders (< 25% serum PSA decrease), and 14% of complete responders. The control cohort had 32% positive biopsy. Nineteen men remain on the biopsy deferral arm. Although the numbers are small and need to be confirmed, these data support a trial of antibiotics in men with elevated PSA as this represents a simple and cost-effective method of decreasing negative biopsies.

One of the recent controversies surrounding serum PSA has been whether it truly reflects cancer or whether benign prostatic hyperplasia (BPH) is the most significant contributor to serum PSA level. Roehl and colleagues[3] studied 1175 men who underwent radical prostatectomy. Prostate size was divided into smaller than 30, 30 to 55, and larger than 55 cc. PSA had a significant correlation with gland volume only in the largest cohort (32% of patients). However, in all groups, serum PSA had a significant correlation with tumor volume. The authors concluded that serum PSA is a better marker for tumor volume than for prostate size.

The isoforms of PSA have been evaluated now for decades. Le and colleagues[4] studied the role of [−2]proPSA, which has been purported to be a more specific marker of prostate cancer. Two thousand thirty-six men were evaluated with total, free, and [−2]proPSA in a screening cohort. Men undergoing biopsy with total serum PSA levels of 2.5 to 10.0 ng/mL were included. Among 63 eligible men, both free and [−2]proPSA predicted malignancy. The area under the curve (AUC) for total, free, and free and [−2]proPSA were 0.50, 0.68, and 0.76 respectively. This modest improvement in overall test accuracy may warrant the addition of a third analyte in routine testing if these data are confirmed in large multicenter trials.

PCA-3 has primarily been used in evaluating men after initial negative biopsy. de la Taille and coworkers[5] evaluated 154 men undergoing initial biopsy (41% had cancer). PCA3 outperformed total and free/total PSA. AUC analysis showed that the specificity for PSA density, free/total PSA, and PCA3 was 0.671, 0.550, and 0.832. These are encouraging findings and if confirmed in larger studies may warrant the use of PCA3 in initial testing.

One of the recent controversies surrounding serum prostate-specific antigen (PSA) has been whether it truly reflects cancer or whether benign prostatic hyperplasia (BPH) is the most significant contributor to serum PSA level.

Ward and colleagues[6] attempted to determine whether PCA3 score in a nomogram would predict low-volume, low-grade prostate cancer. Their nomogram without PCA3 had AUC of 0.727. They evaluated 140 cases from 2 institutions. Insignificant cancers were defined as Gleason score 6 or less and tumor volume smaller than 0.5 cc. Independent predictors included age, PSA density, total length in a core, biopsy Gleason grade, and PCA3 score. A multivariable model demonstrated preservation of significance of age, PSA density, and tumor length, and PCA3 score predicted insignificant cancer. By including PCA3, the AUC increased impressively to 0.926.

Groskopf and associates[7] looked at TMPRSS2:ERG gene fusion in men before prostate biopsy in a multicenter trial. Urine was collected following digital rectal examination (DRE). Prostate cancer was detected in 150 of 339 men. The gene fusion provided a specificity of 86% to 91% and sensitivity of 43% to 50% for the biopsy cohort. Gene fusion was detected in 92% of men who had a positive urine test. This study adds to the emerging data suggesting utility of this genetic variant.

Netto and colleagues[8] provided contrasting information about TMPRSS2:ERG. They studied tissue microarrays of 158 prostate cancers and control tissues obtained at radical prostatectomy that were followed for recurrence. They found that the fusion gene was not associated with progression (biochemical recurrence, clinical evidence of metastases, or prostate cancer mortality). However, ERG gene polyploidy without fusion was a predictor of progression. Whether these differences represent case selection, methodological issues, or other factors, clearly there is need for more investigation before this marker is used clinically.

Albadine and colleagues[9] looked at the TMPRSS2:ERG in minimal prostate cancer (MinPCa; defined as Gleason score 6, < 0.5 cc, single section). Thirty-three men with cancers fulfilling these criteria were compared with

59 routine cancers. The gene fusion was found in 46% of the MinPCa cases and 59% of controls. These were not significantly different. The authors concluded that the lack of a difference in the fusion products argues against its use as a marker of aggressiveness.

Silberstein and colleagues[10] carried out a multicenter investigation of PCA3 and TMPRSS2:ERG gene fusion (T2:ERG) to predict biopsy outcome. First voided urines after DRE were used, and 235 men were investigated. Cancer was detected in 44% of patients. Specificities relative to biopsy of T2:ERG, PCA3, and PSA were 86%, 79%, and 19%, respectively. Logistic regression analysis showed the combination of T2:ERG and PCA3 provided the best performance (AUC 0.761). The enhanced specificity afforded by the combination of these markers should be confirmed in larger trials.

The search for predictors of minimal prostate cancer (amenable for focal therapy or active surveillance) is receiving increased interest, perhaps in part due to the failure of the PLCO screening trial. Leibovici and colleagues[11] evaluated 1526 men undergoing robotic prostatectomy. Minimal disease was defined as less than 5% of the gland involved with Gleason score 6 or less and pT2 cancer exhibiting no perineural invasion. Two hundred forty-one men (16%) had low risk findings. Univariate predictors included lower body mass index, biopsy grade 6 or less, clinical stage T1c, maximum percentage cancer on core, and the percentage of positive cores. Multivariate analysis included Gleason score, percentage of cancer on core, and the percentage of positive cores as predictors. The authors concluded that in men with Gleason score 6 or lower, less than 7.8% of core involvement and fewer than 13.6% positive cores would be expected to have minimal disease and may be candidates for less aggressive therapeutic approaches.

Loeb and colleagues[12] investigated the concept of PSA velocity (PSAV) risk count (the number of times PSAV exceeded a specified threshold) to see whether this predicted progression after radical prostatectomy. Seven hundred eighteen men with at least 3 PSA determinations prior to surgery were evaluated. Adverse pathology was significantly greater in men whose PSAV exceeded 0.4 ng/mL/year more than once. At median follow-up of 97 months, probability was 16% for men fulfilling this risk count definition compared with 8% for those who did not ($P = .0004$). In multivariate analysis, this PSA derivative remained a significant predictor. The Gleason score, however, was a better predictor (odds ratio [OR] 3.7 vs 2.0 for PSAV risk count) in univariate analysis.

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The use of PSAV and PSA doubling time to predict upgrading at radical prostatectomy was studied in 235 men by Krane and colleagues.[13] All men had Gleason score 6 preoperatively and had at least 2 PSA measurements separated by 6 months; 49% of the men were upgraded. On univariate analysis, they had a higher mean PSA and PSA density ($P < .001$). However, on multivariate analysis only biopsy-detected bilateral disease predicted upgrading.

One of the mechanisms for tumor resistance to cytotoxic and other systemic therapies is areas of ischemia and resulting hypoxia. Jans and associates[14] used a tissue microarray from 71 men who had undergone radical prostatectomy. Proteins involved in the Hypoxia Inducible Factor (HIF-1α) pathway were studied. GLUT1, one of the markers studied, predicted shorter time to biochemical recurrence and was independent of grade and stage. Nuclear PHD1 also was associated with worse prognosis. These findings are consistent with the demonstrated role of hypoxia in other malignancies.

Uchio and coworkers[15] investigated cell cycle regulators bcl2 and p53 and markers of angiogenesis to assess their ability to predict prostate mortality. Utilizing a US veteran's database, they identified 1267 men with prostate cancer. During follow-up of 11 to 16 years, 922 men died and 198 were adjudicated to have died of prostate cancer. Prostate tissue was available in 1205 of the men. Adjusting for age and clinical characteristics, bcl2, p53, and microvessel density were significantly associated with prostate cancer mortality ($P = .02$, .01, and $< .001$, respectively). These data are provocative and should be confirmed in other investigations, but they may serve as risk stratifiers for more aggressive therapeutic approaches.

Angiogenesis and resulting increase in microvascularity is an essential component of carcinogenesis and tumor progression. Activation of hematopoietic progenitor cells may precede metastases to lymph nodes. Nakayama and colleagues[16] examined the angiogenic promoter vascular endothelial growth factor receptor 1 (VEGFR1) in lymph nodes obtained at radical prostatectomy. PSA progression was defined as more than 0.2 ng/mL increase. Fifty-nine percent of the lymph nodes negative for metastases were VEGFR1 positive. All

16 of lymph nodes containing prostate cancer were VEGFR1 positive, and 11 of 36 men had PSA recurrence. On univariate analysis, preoperative serum PSA level of 20.0 or higher, Gleason score 7 or higher, and VEGFR1 were predictive of biochemical failure. On multivariate analysis, serum PSA level, Gleason score, and VEGFR1 positivity maintained predictive ability. This observation, if borne out in larger trials, may allow earlier institution of adjuvant therapy in men destined to fail local approaches.

The so-called PSA bounce following brachytherapy is widely recognized. Satoh and colleagues[17] studied this in 388 consecutive patients treated with iodine-125 seed implants without androgen deprivation therapy or external beam radiation. Patients had a minimum of 1 year and 3 serum PSA determinations in follow-up. Three definitions of bounce were used: (a) rise higher than 0.1 ng/mL, (b) rise higher than 0.4 ng/mL, and (c) rise higher than 35% over the previous value followed by a subsequent fall. The actuarial likelihood of experiencing a bounce at 24 months was 50.8%, 23.5%, and 19.4% for definitions a, b, and c, respectively. Clinical stage, pretherapy serum PSA level, and Gleason score did not predict bounce; however, younger age did. This latter finding is intriguing as one of the explanations of the bounce is revascularization of ischemic radiated benign tissue, which may be expected to be greater in younger men.
[Michael K. Brawer, MD]

Screening and Detection

Schröder and colleagues recently reported the results of the European Randomized Study of Screening for Prostate Cancer (ERSPC), in which screening led to a 20% reduction in cancer-specific mortality and a 41% reduction in metastatic disease.[18] In a follow-up study, van Leeuwen and colleagues presented a comparison of the rates of metastatic prostate cancer among screened men from the Rotterdam section of the ERSPC, compared with a population from Northern Ireland where PSA testing is uncommon (6%).[19] At a median follow-up of 10.2 years, the incidence of metastatic prostate cancer was 0.1% in the Rotterdam ERSPC versus 1.1% in Northern Ireland ($P < .0001$). They reported a number-needed-to-treat of 15 to prevent 1 case of metastatic prostate cancer.

The appropriate age to discontinue prostate cancer screening continues to generate controversy. In light of the recent United States Preventive Services Task Force (USPSTF) Guidelines against PSA screening for men over age 75 years,[20] Moul and coworkers[21] examined the public response to this issue in men presenting for a free prostate cancer screening. Of 340 men surveyed, 78% were "upset" by the USPSTF recommendation. Moreover, men aged 75 years or older who underwent radical prostatectomy at their institution had more aggressive pathology features and worse treatment outcomes than patients aged younger than 65 years or 65 to 75 years. These combined findings led the authors to conclude that neither public opinion nor surgical outcomes appeared to support the USPSTF guidelines.

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Another issue related to prostate cancer screening is the disparity in measured PSA levels when different PSA assays are used. Stephan and associates contrasted PSA results using assays standardized against the Hybritech versus the World Health Organization (WHO) standards in 1098 men.[22] In agreement with prior studies,[23] they found that serum PSA levels were 20% to 25% lower using WHO-based assays for total and free PSA. The authors therefore recommended adjusting the PSA threshold for biopsy (eg, from 4.0 to 3.1 ng/mL) when testing with WHO-calibrated assays to avoid missing a proportion of prostate cancers.

Not only are PSA results influenced by assay standardization, but several abstracts described associations between common medications with serum PSA levels. Mener and colleagues[24] reported on serum PSA levels before and after the initiation of statins in 962 men with no history of prostate cancer. Among men in their 50s, 60s, and 70s, the mean reduction in serum PSA levels was 0.16, 0.34, and 0.35 ng/mL, respectively, after starting statin treatment, consistent with prior studies.[25] In a very different population of 1570 men with prostate cancer undergoing radical prostatectomy, Bañez and colleagues reported that H2-blocker therapy was associated with significantly lower serum PSA levels after adjustment for age, race, year, body mass index, surgical center, prostate weight, and pathologic tumor features.[26] Further study is required to explore these findings in men without prostate cancer undergoing PSA screening.

Finally, the ongoing search for new and improved prostate cancer markers continues. Vickers and coworkers previously described the use of a 4-kallikrein panel including total PSA, free PSA, intact PSA, and kallikrein-related peptidase 2 (hK2) for prostate cancer detection.[27] Herein, they reported on the external validation of this panel to predict the results of prostate biopsy.[28] Specifically, the

current study included 2914 men from the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer, who were randomly divided into training and validation sets. Compared with a base model including PSA and age, the addition of the kallikrein markers significantly improved the AUC from 0.64 to 0.76 ($P < .001$) for prostate cancer detection on biopsy in the validation set. The kallikrein panel also improved the discrimination of high-grade prostate cancer, and decision analysis suggested that the use of this model may improve clinical outcomes by reducing the proportion of unnecessary prostate biopsies.

[Stacy Loeb, MD, Alan W. Partin, MD, PhD]

Long-term follow-up of women with stress urinary incontinence shows that injections of autologous muscle cells derived from the quadriceps femoris into various sites around the urethral sphincter complex shows that the procedure resulted in improvement in symptoms in more than 75% of patients treated.

Stress Urinary Incontinence

Autologous Muscle-Derived Cells May Treat Stress Urinary Incontinence

Long-term follow-up of women with stress urinary incontinence shows that injections of autologous muscle cells derived from the quadriceps femoris into various sites around the urethral sphincter complex show that the procedure resulted in improvement in symptoms in more than 75% of patients treated. Results were presented by lead investigator Lesley K. Carr, MD,[29] of the Division of Urology at the University of Toronto and Sunnybrook Health Sciences Center in Ontario, Canada.

The researchers studied the efficacy and safety of muscle-derived cell transplantation. In the study phases, which are ongoing, 29 women (mean age, 49.5 years) whose stress urinary incontinence symptoms had not improved within a year of standard therapy received cystoscope-assisted periurethral cell injections. At the 3-month follow-up appointment, participants could elect a second injection of the same dose.

Follow-up occurred at 1, 3, 6, and 12 months after the last injection. Clinical outcomes were evaluated with a pad weight test, a voiding diary, and validated quality-of-life questionnaires. In the first, double-blind phase, 20 patients were randomized into 5 groups to receive 1, 2, 4, 8, or 16 × 106 autologous muscle-derived cells (AMDCs). In the second, single-blind phase, 9 patients were randomized into 3 groups to receive 32, 64, or 128 × 106 AMDCs.

Results showed that 86.2% of the 29 patients elected a second injection. To date, 17 patients have reached the 12-month follow-up appointment. No serious adverse events have been encountered. Minor events occurred at similar rates among all dose groups and included pain and bruising at the muscle biopsy site, pain at the injection site, mild and self-limiting urinary retention for a few hours without need for catheterization, and urinary tract infection. One patient experienced worsened incontinence several months after injection.

Quality-of-life measures improved in 68% of patients 3 months after the first injection and in 67% of patients 3 months after the second injection. Symptoms improved in 61% of patients at 3 months after the first injection and 3 months after the second injection. Urinary leaks were reduced after both injections. At 12 months, 13 of 17 patients (76.5%) reported an overall reduction in stress leaks and urgency compared with baseline; 4 reported no leaks.

"This study confirms that autologous muscle-derived cells constitute a safe and effective treatment for incontinence at various dosages," said Anthony Atala, MD, an AUA spokesman. "It is important to note that this therapy has few side effects and seems to improve symptoms for most patients in whom other therapies failed."

Botulinum Toxin Injections for Overactive Bladder

The phase II idiopathic overactive bladder prospective, double-blind, placebo-controlled, randomized, multicenter trial conducted in North America and Europe was presented by Dr. Roger Dmochowski[30] as a Late Breaking Abstract.

Current treatment options for patients with overactive bladder (OAB) symptoms refractory to anticholinergics are limited to surgical procedures. There is a strong indication of efficacy for BOTOX® injections (Allergan, Irvine, CA) in neurogenic OAB. The objective of this study was to assess the effects of BOTOX in patients with idiopathic OAB and urgency urinary incontinence (UUI) not adequately managed with anticholinergics.

There is a strong indication of efficacy for BOTOX® injections in neurogenic overactive bladder syndrome.

In this study, 313 patients with OAB and UUI received intradetrusor BOTOX 50 U (n = 57), 100 U (n = 54), 150 U (n = 49), 200 U (n = 53), 300 U (n = 56),

or placebo (n = 44). At baseline, patients had to have 8 or more UUI episodes/week and 8 or more micturitions per day. Detrusor overactivity (DO) was not required, although 76.3% had DO. Symptoms were recorded in a bladder diary. The primary efficacy variable was change from baseline in number of UUI episodes during 7 days before each visit. The primary time point was week 12.

Mean age was 58.8 years; 92% of patients were female. Greater reductions in mean number of weekly UUI episodes were seen with BOTOX versus placebo. A dose-response relationship in the proportions of responders with a 50%, 75%, or 100% reduction in urinary urge incontinence at week 12 was observed. The proportions of patients who experienced a 50% reduction in urinary urge incontinence at week 12 ranged from 70.4% in the 100 U BOTOX group to 83.9% in the 300 U BOTOX group, as compared with 52.3% in the placebo group. The proportions of patients who were incontinence free at week 12 ranged from 29.8% in the 50 U BOTOX group to 57.1% in the 300 U BOTOX group, compared with 15.9% in the placebo group. This dose-response is also observed when the incidence of responders at the defined thresholds at each posttreatment time point is evaluated.

Secondary efficacy variables, including dose-dependent improvements in urodynamic parameters, also showed a positive BOTOX treatment effect. Efficacy was observed in patients with and without DO. Improvements were also reflected in the number of incontinence-free patients at doses of 100 U and higher.

With placebo and BOTOX 50, 100, 150, 200, and 300 U, treatment-related adverse event (AE) rates were 18.6%, 30.4%, 36.4%, 40.0%, 38.5%, and 40.0%. The only AEs significantly higher than placebo were urinary tract infection and retention (postvoid residual [PVR] ≥ 200 mL). Change from baseline in PVR showed dose response, particularly immediately posttreatment and in patients with posttreatment PVR 200 mL or higher.

BOTOX demonstrated significant dose-dependent improvements in urinary symptoms and urodynamic parameters in patients with idiopathic OAB. Improvement in symptoms was reflected in patient perception of benefit. Doses above 100 to 150 U did not appear to add much incremental benefit, particularly when balanced with PVR-related safety parameters. The conclusion of this abstract is that BOTOX demonstrated durable efficacy in idiopathic OAB with dose response on key efficacy and safety parameters. [Naoki Yoshimura, MD, PhD, Michael B. Chancellor, MD]

Lower Urinary Tract Symptoms (LUTS), BPH, and Male Voiding Dysfunction

Of the 2290 abstracts presented at this year's meeting, 100 were presented in sessions dealing with LUTS, BPH, and male voiding dysfunction. In addition, topics relating to BPH and its management were presented in sessions of general epidemiology, cost-effectiveness, and surgical techniques. The presentations were given as either poster or podium in basic science research, epidemiology, marker, and natural history, medical and hormonal therapy, as well as technology and surgical techniques sessions.

Estimates suggest that in 2009 approximately 32.4 million men have histologic BPH, of which 9.4 million are eligible for treatment based on the recommendations of the 1994 BPH Guidelines (AUA Symptom Index greater than 7 representing moderate to severe symptoms and peak urinary flow rate of less than 15 mL/s). Of these, 7.9 million have consulted a physician and 7.2 million are estimated to be under the care of a physician. It is estimated that 4.1 million have been offered and given drug therapy, whereas roughly 140,000 have chosen surgery and 80,000 are estimated to undergo some form of heat-based treatment. Relating to drug treatment, 1 out of every 3 men is estimated to stop BPH medication, perhaps due to lack of efficacy, side effects, or cost associated with the treatment.

Basic Science Research

A total of 20 posters were presented of which some will be discussed in greater detail. Duncan and colleagues[31] presented data regarding the preclinical evaluation of the TRPM8 ion channel agonist D-3263. TRPM8 is a transmembrane cat ion channel protein that is overexpressed in both BPH and in a wide range of cancers, including prostate, breast, lung, and colon cancer. The compound D-3263 induces calcium flux in cells expressing this particular channel protein. The group of investigators from Seattle injected testosterone propionate in rats to induce BPH. The prostate weight increased from 357 to 889 mg (mean) and serum dihydrotestosterone (DHT) increased from 43 to 5984 pg/mL (Table 1). Groups of rats were treated with D-3263 in different dosages. The highest chosen dosage reduced the prostate weight to 648 mg and serum DHT to 175 mg. The 5α–reductase inhibitor finasteride—known to reduce DHT and shrink prostate size—given at 10 mg/kg/day reduced prostate weight to 547 mg and DHT to 89 mg. When combining D-3263 at a dose of 100 mg/kg/day with finasteride at a dose of 10 mg/kg/day, prostate weight was reduced to 435 mg and DHT to 59 pg/mL, levels close to the normal control animals. Immunohistochemical data revealed that combined treatment resulted in nearly normal

Table 1
Prostate Weight and Dihydrotestosterone (DHT) Levels in Control Animals and Animals Treated With D-3263 and Finasteride

Treatment	Control Vehicle (n = 6)	TP/Vehicle (n = 6)	TP/D50 (n = 6)	TP/D100 (n = 6)	TP/D50 + F10 (n = 6)	TP/D100 + F10 (n = 6)	TP/F10 (n = 6)
Prostate weight (mg)	357.3 ± 30.6	889.2 ± 36.3	732.8* ± 23.1	648.0* ± 33.4	569.7* ± 23.3	435.2* ± 20.8	547.0* ± 22
Serum DHT (pg/mL)	43 ± 6	5984.2 ± 718	253.2* ± 44.5	175.1* ± 43.6	100.6* ± 15.2	59.1* ± 10.8	89.0* ± 13.8

TP, testosterone propionate.
Values are presented as mean ± SEM.
*Values lower than TP/vehicle ($P = .004$). Two-sided Mann-Whitney U test was used.
Reproduced with permission from Duncan D et al.[31]

prostate histopathology. Clearly, the TRPM8 agonist D-3263 works in a potentially additive manner with finasteride to reduce the prostate weight induced by treatment with testosterone as well as DHT levels to near normal or control vehicle levels. It is interesting to speculate whether the company (Dendreon Corporation, Seattle, WA) will pursue clinical studies with this particular compound, and, if so, whether the setting will be in monotherapy or in combination with a 5α-reductase inhibitor.

The role of inflammation noted in BPH and other prostate tissue was again the topic of several presentations. Robert and coworkers[32] analyzed 227 prostatectomy specimens from which a tissue microarray (TMA) was constructed. All patients had symptomatic BPH without cancer. The authors found significant prostatic inflammation in 73% of patients with symptomatic BPH versus 20% in the specimens from cadaveric donors without BPH. High inflammation levels were associated with larger prostate volumes and higher International Prostate Symptom Score (IPSS), although age, serum PSA level, and uroflow parameters were not correlated with inflammation levels. The composition of the inflammation was noted to be 37.4% macrophages, 37% T lymphocytes, and 12.9% B lymphocytes.

A group of investigators from Johns Hopkins and the University of San Diego presented 2 abstracts relating to the prostatic monocyte chemotactic protein-1 (MCP-1), which has the potential of representing a novel biomarker for LUTS associated with BPH.[33,34] There is only one publication relating to MCP-1 in the literature.[35] In this article it was shown that MCP-1 is present in a variety of human neoplasm, but not in carcinomatous cells of the prostate. In fact, the authors demonstrated a significantly increased expression of mRNA of MCP-1 in 13 BPH specimens compared with 8 prostate cancer specimens (Figure 1).

Dr. Povlovich from Johns Hopkins and Dr. Parsons from the University of California at San Diego demonstrated by in vitro assays that MCP-1 can be produced by prostatic stromal cells and stimulates prostate epithelial cell proliferation in vitro, an effect that can be blocked by MCP-1 inhibition. They believe this suggests a role of MCP-1 as a locally produced mediator of BPH. Parsons and colleagues[34] analyzed MCP-1 in prostatic fluid

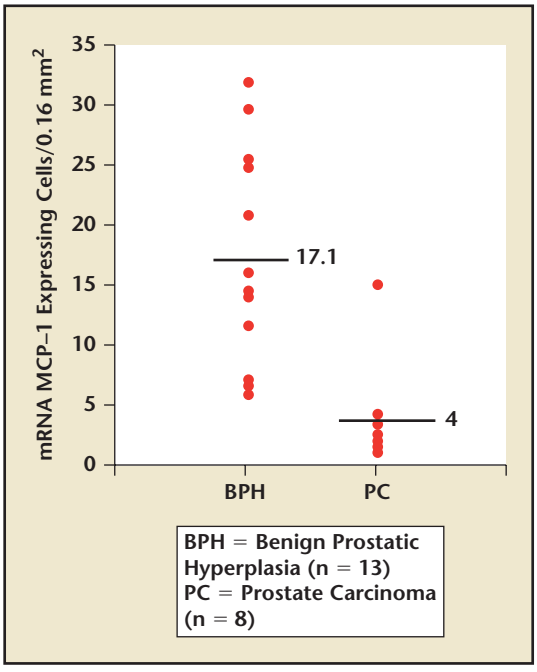

Figure 1. *Number of MCP-1 mRNA–expressing cells in tissue specimens from benign prostatic hyperplasia and prostate cancer (bar = mean). Reproduced with permission from Mazzucchelli L et al.[35]*

and demonstrated by multivariate regression analysis that high IPSS were significantly associated with higher MCP-1 levels. Urine-based data suggested that higher MCP-1 levels also were significantly associated with higher IPSS, but not prostate volume. Obviously, biomarkers for BPH or LUTS are of considerable interest and MCP-1 seems to be a protein holding its own in this regard.

Meng and coworkers[36] examined the impact of androgen deficiency on tight junction architecture in prostatic inflammation. The experimental design presented by this group from Los Angeles and Seattle is quite complex, but fundamentally the authors conclude that the data shown in mice experimentation as well as in prostate biopsies from men with androgen deficiency of the aging male (ADAM) syndrome demonstrate that androgen levels may modulate tight junctions in the prostate leading to a disruption of their architecture and, thus, facilitating inflammatory cell infiltration. Testosterone therapy, on the other hand, appears to restore the integrity of these tight junctions at least in the castrated mice model. The authors believe these results suggest that testosterone supplementation may restore tight junction architecture and thus reverse prostatic inflammatory infiltrates as seen in men with the ADAM syndrome.

Natural History, Markers, and Evaluation

The topic of the use of statin drugs and their potential impact on serum PSA and prostate cancer has received a great deal of attention at this year's AUA meeting. Two abstracts were presented by the group from Rochester, MN, regarding the use of statins as well as nonsteroidal anti-inflammatory drugs (NSAIDs) and the development of urological outcomes, as well as changes in serum benign prostatic specific antigen (BPSA) levels.[37,38]

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St. Sauver and colleagues[37] reported on a clinic cohort of 634 men in the Olmsted County Study. Proportional hazard models were used to determine the associations between medication use and time to development of LUTS, defined as a symptom score greater than 7, flow rate decreased to a level of less than 12 mL/s, or prostate TRUS–measured prostate volume of greater than 3.0 mL. The use of statins in this population was inversely associated with developing LUTS, decreased peak urinary flow rate, and benign prostatic enlargement as defined by prostate volume of over 30 g. The combined use of statins and NSAIDs further decreased the risk for each outcome (Table 2).

Jacobsen and coworkers[38] used BPSA, which is associated with histologic BPH, and found that the regular use of NSAIDs was associated with an estimated hazard ratio of 0.52 in terms of the time of the participants in this study to reach an increased level of BPSA. Based on these data, Jacobsen speculates that the regular use of NSAIDs may in fact be associated with slower growth rates of the prostate as measured by the time to reach an elevated serum BPSA level, in this case, defined at a level above the 75th percentile of the overall

Table 2
Hazard Ratio (HR) of Developing International Prostate Symptom Score (IPSS) > 7, Decreased Flow Rate < 12 mL/s, or Prostate Enlargement > 30 mL in Men With No Medication (Reference Group) and Those Taking Either Statins, Nonsteroidal Anti-Inflammatory Drugs (NSAIDS), or Both

Outcome	No Medications	Statins Only	NSAIDs Only	NSAIDs and Statins
		HR (95% CI)*	HR (95% CI)*	HR (95% CI)*
LUTS	Referent	0.48 (0.34-0.68)	0.44 (0.39-0.49)	0.17 (0.14-0.22)
Decreased Peak Flow Rate	Referent	0.26 (0.15-0.46)	0.31 (0.26-0.38)	0.09 (0.07-0.13)
BPE	Referent	0.44 (0.21-0.94)	0.42 (0.32-0.53)	0.18 (0.12-0.27)

95% CI, 95% confidence interval; BPE, benign prostatic enlargement; LUTS, lower urinary tract symptoms.
*HRs adjusted for baseline age, diabetes, hypertension, coronary heart disease, smoking status, and weight.
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population. This adds to the growing body of evidence that NSAIDs in some way protect against clinical BPH, but the exact mechanism of action is not yet fully understood.

Two groups of authors, from Korea[39] and Egypt,[40] reported on anatomic variations of the prostate, specifically the angle between the bladder base/neck and the urethra, as a predictor for bladder outlet obstruction. Although of some interest, it was discussed after the presentation that such an angle might be heavily dependent on the status of bladder filling as well as the presence or absence of a catheter and may not be of great practical value at the moment.

Merino and colleagues[41] reported data on a large database (Health Improvement Network or THIN) from the United Kingdom in which over 700,000 men provided information through their general practitioners. In this database, 1844 cases of probable acute urinary retention were identified and matched with 10,000 control patients. The relative risks of acute urinary retention to occur in this cohort were increased for men with the diagnosis of "prostatism" (RR 1.7), BPH (RR 2.1), prostate cancer (RR 1.9), and a variety of other urological conditions. The main purpose was to examine the role of antimuscarinic agents and the timing thereof on the onset of acute urinary retention episodes. The relative risks for acute urinary retention when such a drug was given for a urogenital indication was 4.0 and, thus, highly significant. The relative risk was particularly high in those men who had taken the antimuscarinic very recently, within the last 30 days. Overall, in these patients, the relative risk was 8.3 versus 2.0 in those having taken it between 1 month and 12 months or longer than 1 year in the past. Relative to the indication, the greatest risk existed in those men taking an antimuscarinic for urogenital indication within less than 30 days; the relative risk was 14.2 (Table 3).

The finding that the risk of acute urinary retention in men given antimuscarinics for a urogenital indication is increased in such a manner depending on indication, duration, and dosage is practical information

Table 3
Relative Risk of Acute Urinary Retention (AUR) by Treatment Indication, Duration, and Dose

	Number (%) of Patients			
	Cases (n = 1844)	Controls (n = 10,000)	Relative Risk†	95% CI
Use				
Nonuse	1706 (93)	9727 (97)	1	
Current use	94 (5)	154 (2)	2.9	2.2-3.7
Indication‡: Current Use				
Antispasmodic	6 (8)	20 (17)	1.2	0.5-3.1
Drug-induced parkinsonism	8 (10)	22 (19)	2.0	0.9-4.5
Urogenital	64 (82)	74 (64)	4.0	2.8-5.7
Duration/Indication*: Current Use				
≤ 30 d urogenital	29 (37)	10 (9)	14.2	6.8-29.6
≤ 30 d non-urogenital	4 (5)	8 (7)	2.6	0.8-8.9
> 30 d urogenital	35 (45)	64 (55)	2.5	1.6-3.8
> 30 d non-urogenital	10 (13)	34 (29)	1.4	0.7-2.8
Daily Dose/Indication: Current Use				
Low/medium dose urogenital	59 (76)	69 (59)	3.9	2.7-5.6
Low/medium dose non-urogenital	11 (14)	34 (29)	1.6	0.8-3.1
High-dose urogenital	5 (6)	5 (4)	5.6	1.6-20.0
High-dose non-urogenital	3 (4)	8 (7)	1.7	0.4-6.6

95% CI, 95% confidence interval.
*Percentages for nonuse and current use are based on overall study cohort (1844 cases; 10,000 controls); percentage for indication, duration/indication, and daily dose/indication are based on the number of patients currently using antimuscarinics who had a known indication (78 cases, 116 controls).
†Relative risk estimates were adjusted for age, calendar year, and general practitioner visits.
‡Among current users, 16 of 94 cases and 38 of 154 controls had unknown indications.
**Antispasmodic and drug-induced parkinsonism were grouped under non-urogenital.
Reproduced with permission from Roehrborn CG et al.[42]

for any physicians managing patients with LUTS and BPH in their clinic. Clearly, men with such risk factors should be closely monitored when given an antimuscarinic agent, presumably by measurement of postvoid residual urine volume before and within a month or 2 after initiation of therapy.

Roehrborn and colleagues[42] presented data from a placebo-controlled invasive urodynamic assessment in a multicenter trial in men with LUTS and BPH who were given 12 weeks of daily tadalafil (20 mg) versus placebo. Although the primary objective of this particular study was to document the effect of 20 mg of tadalafil on urodynamic parameters, the patients in the placebo group were analyzed regarding the reproducibility of invasive pressure-flow parameters versus noninvasive free urinary flow rate and postvoid residual measurements. The change from baseline to endpoint for P_{DET} at Q_{max} was 0.1 with an interquartile range (IQR) of 18.5. For the bladder outlet obstruction index (BOOI), the change was −1.0 with an IQR of 22.7. The intubated flow rate had a correlation coefficient from baseline to endpoint of 0.82, whereas there was a greater variability observed with the free urinary flow rate (correlation coefficient 0.55). The data suggest that in a properly conducted and multicenter trial with standardized urodynamic protocol and a central reader, invasive urodynamic studies can be extraordinarily reproducible and, in fact, more so than free flow rates, postvoid residual checks, or subjective measures such as the symptom score. Data from this trial should allow any investigator interested in conducting such a trial to use the key statistical parameters for appropriate sample size and power calculations (Table 4).

Medical and Hormonal Therapy

Helfand and colleagues[43] from Northwestern University in Chicago analyzed the IMS Health dataset that includes integrated medical and pharmacy data from 90 US health care plans. They accessed administrative claims data from October 2006 to September 2007 and focused on patients with LUTS and OAB identified by specific diagnoses codes. Patients who filled prescriptions were considered as "treated," whereas patients who did not fill prescriptions were considered as "untreated." In a population of 8,718,192 men diagnosed with BPH by ICD-9 code, 33.6% were treated with the prevalence of treatment increasing by age from 19% for men aged 45 years to 54% to 43% for men 65 years or older. The most commonly used drugs were α-adrenergic receptor blockers followed by 5α-reductase inhibitors and a respectable number of men were on anticholinergic medication (12.3%). The most common drug prescribed was tamsulosin, accounting for nearly 50% of all medications, followed by doxazosin and alfuzosin as well as terazosin with roughly 48% for each, and finasteride (17.1%) and dutasteride (14.1%). Patients with increased comorbidities were significantly more likely to be treated and treatment also varied as a function of physician specialty. For example, 40% of all patients seen and treated by a urologist were treated versus 29% of patients seen by primary care providers and 37% of those seen by nephrologists. In a second analysis, the same group of investigators identified 7,244,501

Table 4
Baseline, Endpoint, Change From Baseline, and Correlation Between Baseline and Endpoint as Well as Interquartile Range (IQR) for Key Parameters of Pressure Flow and Noninvasive Assessments

	Baseline		Endpoint		Change		Correlation Baseline-Endpoint	
	Mean ± SD	IQR	Mean ± SD	IQR	Mean ± SD	IQR	n	r
$P_{DET}Q_{max}$ (cm H_2O)	54.9 ± 27.6	28.2	55.0 ± 24.3	30.6	0.1 ± 15.5	18.5	89	0.83
BOOI	36.0 ± 31.2	33.2	35.1 ± 27.9	34.3	−1.0 ± 18.2	22.7	89	0.82
Pressure-flow Q_{max} (mL/s)	9.5 ± 5.0	5.5	10.0 ± 4.9	5.2	0.5 ± 2.9	2.6	89	0.82
Free-flow Q_{max} (mL/s)	13.3 ± 7.5	8.4	13.6 ± 9.0	6.5	0.5 ± 8.0	5.8	76	0.55
PVR (mL)	62.1 ± 68.0	85.0	62.3 ± 87.2	80.0	−1.8 ± 86.6	52.5	68	0.42
IPSS	22.0 ± 5.8	9.0	16.9 ± 7.0	11.0	−5.1 ± 7.0	9.0	89	0.41

BOOI, bladder outlet obstruction index; IPSS, International Prostate Symptom Score; PVR, postvoid residual volume.
Reproduced with permission from Roehrborn CG et al.[42]

patients diagnosed with overactive bladder of which 24% were diagnosed and treated, whereas 76% were left untreated.[43] The diagnosis and treatment decisions also varied as a function of physician specialty, with 18% of patients seen by primary care physicians being treated versus 31% of patients seen by urologists and 18% seen by obstetrician-gynecologists. The proportion of men treated was significantly less than female patients treated (16% vs 24%), which held true after adjusting for age. Specific to those 3,247,112 men diagnosed with OAB of which 16% were treated, a significant increase in the prevalence of treatment was seen by age group.[44] Eleven percent of men aged 45 to 54 years were treated versus 14% of men aged 55 to 64 years and 21% of those aged 65 years and older. The most commonly prescribed medication in descending order were tolterodine, oxybutynin, tricyclic antidepressants, solifenacin, darifenacin, and others. Patients with more comorbidity were more likely to be treated and urologists were more likely to prescribe medications compared with other specialties. Overall, the analyses presented by Helfand and colleagues is quite illuminating in regard to the prescribing habits of physicians of various specialties for a wide spectrum of middle-aged and elderly men and women with OAB and for LUTS and BPH, suggesting that a very significant proportion of these patients remain untreated. The reasons for undertreatment remain unclear and perhaps are related to bother due to symptoms.

A somewhat similar study was presented by Sarma and colleagues from Michigan, who reported on the Olmsted County Study of Urinary Symptoms in Men.[45] Over a 10-year follow-up of men in this particular cohort who were prescribed medication for LUTS, 41% of men remained on medication, whereas 50% stopped the medication and 9% required surgery for BPH. The likelihood of surgery following medication use was associated with increased bother at the time of first medication use (HR 2.19) and with a decreased peak urinary flow rate (HR 3.26). Interestingly, the likelihood of surgery did not increase with increased prostate volume, elevated PSA, elevated overall symptoms, or older age. It does appear apparent that, at least in this cohort of men from Olmsted County, physicians and patients together embark on a decision for surgery based on symptom bother and more often based on flow rate readings compared with prostate volume or serum PSA measurements.

It does appear apparent that, at least in this cohort of men from Olmsted County, physicians and patients together embark on a decision for surgery based on symptom bother and more often based on flow rate readings compared with prostate volume or serum PSA measurements.

Kaplan and coworkers[46] reported on an interesting observation that prompted them to study a population of 212 consecutive men seen in the Urology Clinic at Cornell University in New York. These men were switched by their primary care physician, usually for insurance coverage reasons, from a branded medication for LUTS/BPH to generic medications such as terazosin, doxazosin, or finasteride. The overall observation was that there were more new-onset side effects in patients switched from branded to generic α-blockers as well as those switched from branded 5α-reductase inhibitors to generic finasteride. Conversion from branded Uroxatral® (Sanofi-Aventis, Bridgewater, NJ) and Avodart® (GlaxoSmithKline, Philadelphia, PA) resulted in the greatest decrease in efficacy with 48.6% and 29.6% of patients having significant changes, whereas conversion from Flomax® (Boehringer Ingelheim, Ridgefield, CT) and Proscar® (Merck, Whitehouse Station, NJ) to generic α–blockers and finasteride resulted in the greatest increase in new-onset adverse events (Table 5).

This is an important observation that will need to be corroborated in

Table 5
Changes in Lower Urinary Tract Symptom Measures After Switching From Branded to Generic Medications

	Branded AB at Baseline N = 148	Generic AB at 8 weeks	Branded 5ARI at Baseline N = 64	Generic 5ARI at 8 weeks
IPSS	7.6	16.9***	14.9	17.3*
Q_{max} (mL/s)	10.7	9.7*	10.3	9.5*
PVR (mL)	54	46	34	53*
Frequency 24 h	8.7	9.5*	7.8	8.3
IIEF	20.5	16.6***	21.4	16.2*

5ARI, 5-α reductase inhibitor; AB, α-blocker; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; PVR, postvoid residual volume.
Data are presented as mean values unless stated otherwise. *$P < .5$, **$P < .1$, ***$P < .001$.
Reproduced with permission from Kaplan SA et al.[46]

larger datasets. Generic drugs approved in the United States have to show bioequivalency in a very small number of subjects, and the active ingredient contained in each tablet may vary from 75% to 125% of the label. Whether absorption differences exist leading to decreases in efficacy and increases in adverse events is an untested hypothesis, but worthy of further investigation.

At last year's meeting, a dose-ranging study was reported and later published in *The Journal of Urology* examining the efficacy and safety of tadalafil at 2.5, 5, 10, and 20 mg once daily against placebo in men with LUTS and BPH. The 5-, 10-, and 20-mg doses were found to be superior in terms of symptoms score, BPH Impact Index, and quality-of-life improvement with no measureable effect on peak urinary flow rates. Subsequent to the study, a multicenter urodynamic study was performed in 200 patients randomized to either placebo or 20 mg of tadalafil.[47] All patients underwent invasive urodynamic testing and the primary outcomes were urodynamic parameters such as P_{DET} at Q_{max} and bladder outlet obstruction index. There were no significant changes in either free flow assessment or postvoid residual volume measurement, nor were there any significant changes in the assessment obtained by invasive pressure-flow testing such as P_{DET} at Q_{max}, intubated flow rate, and BOOI (Table 6). However, the tadalafil-treated patients experienced significantly greater symptom improvement and a trend was noticed toward a lower proportion of men in the tadalafil group being obstructed compared with the placebo group at the end of the 12-week study (Figure 2).

An additional report from this 5-arm, multicenter, randomized, placebo-controlled, dose-finding study found that the presence or absence of erectile dysfunction (ED) and the response of ED to treatment with tadalafil did not impact upon the efficacy of tadalafil for the improvement of LUTS as measured by the IPSS, BPH Impact Index, or other humanistic questionnaires[48] (Figure 3). This is an important observation as one hypothesis might have been that the overall improvement in ED would lead to an overall improvement of quality of life associated with measurable changes in IPSS. The absence of such correlation suggests, however, that tadalafil works independent of the presence or absence of ED and/or the presence or absence of a measureable effect on the IIEF in terms of improvement in LUTS-related symptoms.

A new α-blocker was introduced that had recently received approval in the United States for the use in men with LUTS secondary to clinical BPH. This new α-blocker is silodosin, marketed by Watson Pharma Inc. (Morristown, NJ) under the brand name of Rapaflo™. This uniquely α_{1A}-selective α-blocker with a 162-fold selectivity for α_{1A}- over the α_{1B}-receptor has been developed by a pharmaceutical company in Japan and was recently acquired by Watson Pharmaceuticals

Table 6
Mean at Baseline (BL) and Endpoint (EP) for Various Urodynamic Parameters in the Placebo and Tadalafil 20 mg Daily Group

	Placebo (N = 89)				Tadalafil 20 mg (N = 83)			
Measure								
Free-Flow Assessments	n	BL	n	EP	n	BL	n	EP
Peak flow rate	82	13.32	80	13.56	72	15.50	74	15.25
Postvoid residual volume by catheterization	73	62.07	71	62.27	69	52.57	71	43.51
Total bladder capacity	72	333.11	70	305.34	68	323.09	70	312.90
Bladder voiding efficiency	72	83.46	70	82.18	68	85.07	70	86.77
Pressure-Flow Assessments								
$P_{DET}Q_{max}$	89	54.90	89	55.03	83	56.18	83	54.11
Peak flow rate	89	9.45	89	9.98	83	10.31	83	10.68
Bladder outlet obstruction index	89	36.00	89	35.07	83	35.57	83	32.75

Reproduced with permission from Dmochowski RR et al.[47]

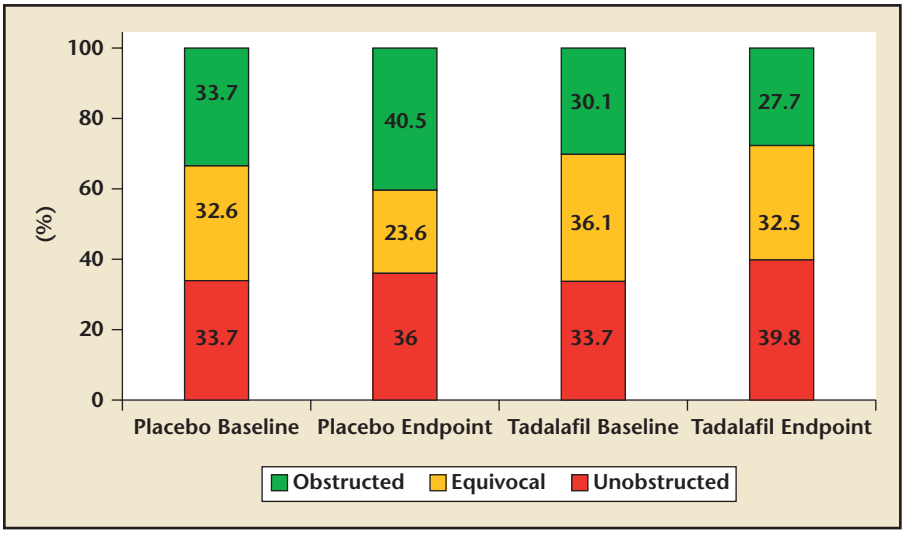

Figure 2. *Proportion of men categorized as obstructed, equivocal, or unobstructed by pressure flow studies before and after 12 weeks of treatment with placebo versus 20 mg of tadalafil daily. Reproduced with permission from Dmochowski RR et al.*[47]

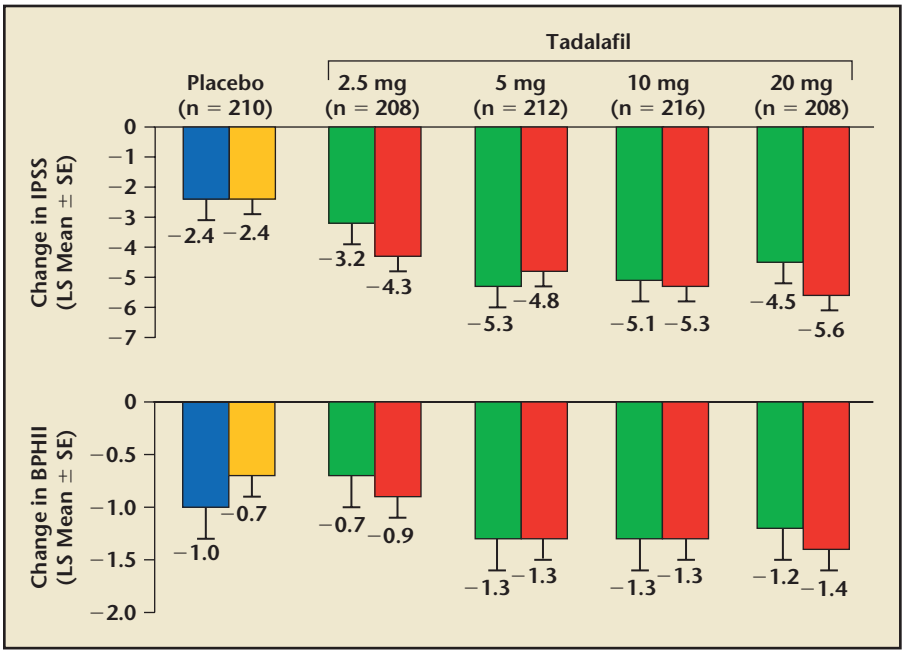

Figure 3. *Change in International Prostate Symptom Score (IPSS) and BPH Impact Index (BPHII) stratified by erectile dysfunction (ED) status at baseline. Reproduced with permission from Broderick G et al.*[48]

and studied in 2 phase III randomized, placebo-controlled trials of 12 weeks duration as well as a 52-week open-label extension study. A group from Japan[49] reported on the early efficacy of silodosin on both storage and voiding function based not only on subjective questionnaires, but also on pressure-flow studies. The patients in the study had an improvement in their symptom score from 17.8 to 9.8 points, and their quality-of-life score dropped from 5.1 to 3.2 points. Peak urinary flow rate improved significantly from 7.5 to 11.3 and it was noted that on pressure-flow studies, maximum cystometric capacity increased, as was the first desire to void (from 127 to 159 mL). Uninhibited detrusor contractions disappeared in 14 of 21 patients after administration. The authors also observed a surprisingly large decline in PDET at Q_{max} from 73.9 to 52.4, which was highly significant and suggestive of an un-obstructing effect of silodosin.

Another group from Japan[50] reported on a trial in which the main emphasis was the study of bothersome nocturia in patients who had been therapy resistant, that is, who failed on other LUTS medications. In this study of 85 patients, an improvement in both storage and voiding symptoms was observed and nocturia as an isolated symptom improved significantly at 4 weeks.

The 2 US studies were presented by Marks and colleagues.[51] A rapid and sustained improvement in both irritative and obstructive symptoms was reported after only 3 days of treatment by using a modified IPSS score in this pooled dataset from both phase III trials involving a total of 466 silodosin and 457 placebo-treated patients. The authors reported for all 7 questions of the IPSS score statistically significant improvements against placebo at the 3-day questionnaire administration, with the exception of nocturia, which was significant after 1 week with a difference of −0.5 for silodosin and −0.3 for placebo.

An interesting question was raised by Roehrborn and coworkers[52] when they studied the approximately 28% of patients experiencing ejaculatory disturbances while on silodosin treatment. An analysis of this subset of patients demonstrated that the patients experiencing ejaculatory disturbances had a greater improvement both in their overall and irritative and

obstructive symptoms subscores, and an overall greater improvement in the maximum urinary flow rate. Both groups, those with and those without ejaculatory disturbances, experienced statistically greater improvement versus placebo, whereas the difference between those with versus those without ejaculatory disturbances was not statistically significant, but numerically of interest. For example, the change in IPSS from baseline to 12 weeks was 3.5 in the placebo group, 6.1 in the patients without ejaculatory disturbances, and 7.2 in those with ejaculatory disturbances. Peak urinary flow rate improved by 1.5, 2.4, and 3.1 mL/s, respectively. A further analysis was done by responder analysis (Table 7).

The responder analysis was based on a subset of patients achieving a 30% improvement in both symptoms and flow rate or a 3-point improvement in symptoms and a 3-mL/s improvement in the peak urinary flow rate. When focusing on these subgroups, the responder threshold analysis suggests that in regard to the 30%/30% improvement, 9.5% of placebo-treated patients versus 22% of patients who experienced no ejaculatory disturbances versus 30.6% of patients who did experience ejaculatory disturbances achieved this goal with the odds ratio being significant for both treatment groups against placebo (2.67 and 4.18, respectively for the patients without and with ejaculatory disturbances), whereas the odds ratio was 1.57 for those with versus without ejaculatory disturbances. Considering the responder analysis regarding the 3 points/3-mL/s improvement, the percentages were 13.1%, 23.7%, and 34.2% for the 3 treatment groups, respectively. Both treated patient groups had favorable odds ratios against placebo and the patients with ejaculatory disturbances had an odds ratio of 1.68 ($P = .0321$) against those without ejaculatory disturbances. This analysis suggests that ejaculatory disturbances under the highly α_{1A}-selective adrenergic receptor blocker, silodosin, are associated with relaxation of the smooth muscle leading to greater improvement in overall symptoms, as well as obstructive symptoms and urinary flow rate improvements. Regarding improvements in the obstructive subgroup of the IPSS score, it was noted that the improvement in the placebo group was 2.1 versus improvement in the patients without ejaculatory disturbances (3.8) and in those with ejaculatory disturbances (4.6), representing an improvement that is more than double of that in the placebo group (data based on pooled analysis).

In recent years, the injection of intraprostatic botulinum toxin has received a great deal of attention based on single-center or single-investigator (usually) uncontrolled trials in which a significant improvement in symptoms, but also often a significant reduction in prostate size and a decrease in serum PSA, was reported. The manufacturer of botulinum toxin type A (BoNT-A), Allergan, is conducting a worldwide multicenter randomized and sham-controlled trial at the present time. The National Institute of Diabetes and Digestive and Kidney Diseases Minimally Invasive Surgical Therapies (NIDDK MIST) study group has conducted a 12-week phase II trial utilizing 100 and 300 U of BoNT-A in patients with LUTS and BPH and has reported their findings in several abstracts at this year's meeting.[53,54] The trial design was a 2-arm, randomized, double-masked,

Table 7
Odds Ratio (OR) for Achieving a 30% Improvement in International Prostate Symptom Score (IPSS) and Q_{max} for Men Treated With Placebo Versus Silodosin Further Stratified by Patients With No Ejaculatory Versus Those With Ejaculatory Disturbances (No RE vs RE) (Upper Panel); OR for Achieving a 3-Point Improvement in IPSS and a 3 mL/s Improvement in Q_{max} for Men Treated With Placebo Versus Silodosin Further Stratified by Patients With No Ejaculatory Versus Those With Ejaculatory Disturbances (No RE vs RE) (Lower Panel)

30%/30%	Placebo (457)	No RE (335)	RE (131)
Responder	9.5%	22%	30.6%
OR vs placebo		2.67 <.0001	4.18 <.0001
OR RE vs no RE			1.57 .0714
3 points/3 mL/s	**Placebo (457)**	**No RE (335)**	**RE (131)**
Responder	13.1%	23.7%	34.2%
OR vs placebo		2.05 .0003	3.45 <.0001
OR RE vs no RE			1.68 .0321

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Table 8
Primary Outcomes of National Institute of Diabetes and Digestive and Kidney Diseases Minimally Invasive Surgical Therapies Botulinum Toxin Type A Trial

	100 U	300 U
AUA symptom score		
• Difference (12 wk−baseline)	−6.1	−8.7
• Percentage change from baseline	−32.4%	−42.1%
Q_{max} (mL/s)		
• Difference (12 wk−baseline)	2.1	2.8
• Percentage change from baseline	25.6%	28.4%

AUA, American Urological Association.
Reproduced with permission from Crawford DE et al.[53]

phase II trial in which the 2 dose levels were not compared with each other, but compared with a predetermined critical cutoff value, namely an improvement of 30% in both symptoms and flow rate as a measure of success. The trial was conducted in 7 academic clinical centers across the United States and included 131 patients. Table 8 shows the main outcomes, namely an improvement in symptom score from baseline to 12 weeks of 6.1 points for 100 U a day, 8.7 points for 300 U, and an improvement in peak urinary flow rate of 2.1 and 2.8 mL/s, respectively. Adverse events were minor. Interestingly, patients treated experienced somewhat unexpectedly an improvement in ejaculatory function, with a decrease in the ejaculatory function questionnaire from a baseline of 10.06 by −2.38 points (for the 100 U group) and from a baseline of 9.52 by −2.07 points (for the 300 U group), both changes being highly significant. The mechanism of improvement in ejaculatory function in the absence of any measurable changes in erectile function as reported in the same abstract remains unclear, and is of considerable interest for further detailed analysis.

The MIST study group also examined the role of the intravesical prostatic protrusion (IPP) and its impact on the magnitude of improvement following BOTOX injection. The results suggest that patients with a pronounced intravesical prostatic protrusion, that is, larger than 5 or 10 mm, experience less symptomatic improvement compared with those with a lesser or absent intravesical protrusion (Table 9). Further analysis from both the NIDDK MIST study and the Allergan-sponsored worldwide trial may be expected later this year.
[Claus G. Roehrborn, MD, FACS]

Obesity and Nephrolithiasis

Obesity and nephrolithiasis were a common theme of the kidney stone papers delivered at this year's meeting. Therefore, an overview of these papers is presented, including papers that focused on metabolic factors as well as those that deal with stone removal in this population.

Epidemiologic studies have previously demonstrated that obesity is a risk factor for the development of kidney stones.[55] The fat deposition that is present in this cohort may be in subcutaneous tissue or in the visceral compartment. Fujimura and colleagues[56] performed a retrospective, case-control study of stone formers and age/gender–matched stone formers who had been subjected to a computed tomography scan. The visceral fat area and abdominal circumference of male and female stone formers were significantly greater than the nonstone formers. A multivariate analysis demonstrated that visceral

Table 9
International Prostate Symptom Score (IPSS) and BPH Impact Index (BPHII) Improvements Stratified by Intravesical Protrusion (IPP) Parameter

	IPSS		BPHII	
IPP (mm)	Baseline Mean	Change at 12 wk	Baseline Mean	Change at 12 wk
0-1	20.3	−9.3	5.7	−3.4
> 1-6	18.0	−7.7	5.0	−2.8
> 6-10	19.9	−7.3	5.2	−2.7
> 10	21.0	−5.5	5.4	−1.7
Overall	19.5	−7.5	5.3	−2.7

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fat accumulation was a significant risk factor for stone formation in males.

Obesity is a surrogate for metabolic syndrome. Previous studies have demonstrated a link between this disorder and uric acid stone formation.[57]

Desai and associates[58] assessed the impact of body mass index on urinary stone risk parameters and stone composition. There was a positive correlation between body mass index and sodium, phosphate, and urea nitrogen excretion. They demonstrated that with increasing body mass index the likelihood of a stone former having uric acid stones increases.[58] This corroborates that metabolic syndrome/obesity is a risk factor for uric acid stone formation.[57,59,60]

There was a positive correlation between body mass index and sodium, phosphate, and urea nitrogen excretion.

Contemporary bariatric surgery, namely Roux-en-Y gastric bypass and duodenal switch procedures, has been linked to stone formation. A significant number of patients subjected to these procedures have hyperoxaluria after surgical intervention.[61] The timing of the development of hyperoxaluria in this cohort has not been well defined. Park and colleagues[62] reported on 45 morbidly obese patients undergoing Roux-en-Y gastric bypass who collected 24-hour urine specimens before and at 6 to 12 months after this procedure. The median urine oxalate excretion increased from 32 mg to 40 mg. In addition, citrate excretion and urine volume decreased significantly and the supersaturation of calcium oxalate increased significantly during this interval. This suggests that risk factors for stone formation develop in the first year after this procedure.

Contemporary bariatric surgery, namely Roux-en-Y gastric bypass and duodenal switch procedures, has been linked to stone formation.

The reduction in mortality and the eradication of medical comorbidity associated with bariatric surgery combined with the epidemic of obesity in the United States and other countries will increase bariatric surgical volume. A looming question is whether restrictive bariatric procedures such as gastric banding will also increase stone risk. Penniston and associates[63] evaluated 27 patients undergoing laparoscopic Roux-en-Y gastric bypass and 11 subjected to laparoscopic gastric banding with 24-hour urine collections most commonly obtained 2 to 3 years after these procedures. Urine volume was low in both groups, whereas calcium excretion was higher in those subjected to gastric banding. The prevalence of hyperoxaluria and hypocitraturia was higher in the Roux-en-Y cohort. These results suggest that laparoscopic gastric banding may have less of an impact on stone risk as compared with Roux-en-Y gastric bypass, and hence may be the preferred bariatric procedure for those with a history of nephrolithiasis.

There have been reports of oxalate nephropathy developing in patients subjected to Roux-en-Y gastric bypass.[64] Animal models may provide insight into why this problem develops and how best to prevent it. Canales and colleagues performed Roux-en-Y gastric bypass in diet-induced obese rats. The kidneys of these animals had increased renal tubular mineral deposition, interstitial inflammation, glomerular changes, and expression of osteopontin and macrophage mononuclear cell stain as compared with controls. These findings suggest that inflammatory and immunologic mechanisms may be involved in renal injury after Roux-en-Y gastric bypass.[65]

Stone removal may be challenging in obese patients. Various reports at this meeting addressed stone removal in this cohort. Ray and associates[66] reported on factors that influence success with shock wave lithotripsy (SWL). Increasing skin-to-stone distance, a parameter linked to body mass index, was a risk and a significant predictor of SWL failure in a multivariate analysis.[66] The utilization of the blast path during SWL with the Dornier HM3 lithotripter allowed SWL to be effective in obese patients.[67] Pishchalnikov and colleagues[68] demonstrated in an in vitro model that lithotripters vary in their ability to fragment stones at different depths along the acoustical access and thus for certain lithotripters that effective fragmentation occurs outside of F2. Therefore, success with SWL in obese patients may be lithotripter dependent.[68]

Ureteroscopic stone removal may be an effective method for removing stones in obese patients. This was demonstrated in a multi-institutional study reported by Chew and associates[69] in which results of ureteroscopic stone removal in 152 obese, 69 overweight, and 44 with a body mass index lower than 25 were analyzed. The stone-free and complication rates were similar among all 3 cohorts.[69] Percutaneous nephrostolithotomy (PCNL) is an effective method of stone removal. Bagrodia and colleagues[70] analyzed factors that impacted complete costs and clinical results with PCNL. Body mass index was not

associated with costs or clinical results. The only factor that influenced complete cost was stone burden; large stones consumed more economic resources without impacting morbidity.[70]

These aforementioned reviewed studies provide insight into the mechanisms of stone formation in obese individuals. Furthermore, they demonstrate that excellent results are achievable with this cohort.
[Dean G. Assimos, MD]

Urologic Chronic Pelvic Pain Syndromes (UCPPS)

Although many cases of chronic prostatitis (chronic prostatitis/chronic pelvic pain syndrome or CP/CPPS) and interstitial cystitis (interstitial cystitis/painful bladder syndrome or IC/PBS) still undoubtedly involve the prostate and bladder, respectively, it is becoming apparent, based on the 2009 AUA meeting presentations, that clinical research is looking beyond organ centricity. Epidemiologic and clinical studies are shifting to examining the psychosocial and systemic manifestation of these conditions and examining therapies that impact outside the prostate and bladder. It is becoming apparent that there is a significant shift in our attempt to understand these conditions as syndromes with multiple clinical phenotypes, rather than homogenous groups of patients with similar etiologic mechanisms and clinical manifestations.

IC/PBS and CP/CPPS

Clemens and the Urologic Pelvic Pain Collaborative Research Network have developed a genitourinary pain index (GUPI) for men and women with urologic pain conditions.[71] The GUPI was developed from the National Institutes of Health (NIH) chronic prostatitis symptom index with 2 additional questions about bladder discomfort in women; the male-specific pain questions were changed to female-specific questions. The GUPI was validated and discriminated well between men with CP/CPPS and IC/PBS and women with IC/PBS and those without these diagnoses. The GUPI was highly responsive to change and was similar in both male and female responders. The GUPI is a single instrument that we will be able to use to assess the degree of symptoms in both men and women with genitourinary pain complaints.

Whitmore[72] presented a state-of-the-art lecture on the overlap between prostatitis and other pelvic pain syndromes. The most common overlap, of course, is IC/PBS, but other pain syndromes including scrotal pain, urethral/penile pain, gastrointestinal causes of pelvic pain, pelvic floor muscle dysfunction, and pudendal neuralgia are also commonly associated. Men with CP/CPPS also report pain with ejaculation and less sexual pleasure and satisfaction. The association between other medical conditions such as fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome, which is certainly very prevalent in women with IC/BPS, is likely less in men with CP/CPPS. The NIH Multidisciplinary Approach to Pelvic Pain (MAPP) Research Network is set to address chronic pelvic pain in a multidisciplinary, collaborative, multisite, basic, translational, and clinical research fashion.

In a late-breaking research session, Nickel and Shoskes proposed that although all patients with IC/PBS and CP/CPPS appear initially similar, each patient is in reality a unique individual (the snowflake hypothesis).[73] The investigators have developed a clinical phenotyping strategy, categorizing patients into 6 UPOINT domains. It was hypothesized that IC/PBS and CP/CPPS patients represent truly unique individuals with varying etiologies, symptom complexes, and progression trajectories. The investigators further hypothesized that patients could be easily classified, employing standard clinical assessment, into the UPOINT domains (urinary, psychosocial, organ specific, infection, neurologic/systemic, tenderness). The researchers noted that they were able to categorize 100 consecutive IC/PBS and 90 consecutive CP/CPPS patients into the UPOINT system employing standard clinical assessment (plus some further questionnaires for psychosocial domains). The researchers concluded that UCPPS patients are, indeed, unique, and that they can be clinically classified in the UPOINT system. They further noted that the duration of symptoms, but not age, correlates with a number of phenotypic domains, whereas the number of domains correlates with severity of symptoms. They also found the domains outside the bladder and prostate (psychosocial, neurologic/systemic, and tenderness) actually have the most impact on symptoms and quality of life. They raised the possibility of phenotypically targeted therapy as the future for the treatment of UCPPS.

Food sensitivities are believed to be associated in exacerbations of symptoms in both IC/PBS and CP/CPPS patients.

Food sensitivities are believed to be associated in exacerbations of symptoms in both IC/PBS and CP/CPPS patients. Herati and colleagues[74] compared the prevalence of food sensitivity between IC/PBS (n = 325) and CP/CPPS (n = 260) patients. Based on a validated dietary questionnaire, the investigators noted that

IC/PBS patients were more likely than CP/CPPS patients to have food and beverage sensitivity. The most bothersome comestibles among both groups included coffee, spicy foods, alcoholic beverages, tea, citrus foods, and hot peppers.

IC/PBS

Barry and colleagues[75] reported on the Rand Interstitial Cystitis Epidemiology (RICE) study, designed to develop an epidemiologic definition of IC/PBS and to use that definition to estimate the prevalence of IC/PBS in US women. The investigators developed a high sensitivity definition (sensitivity 81%, specificity 54%) and a high specificity definition (sensitivity 48%, specificity 83%) by conducting interviews in 599 adult women with IC/PBS and overactive bladder, endometriosis, or vulvodynia. Based on a national telephone survey of approximately 100,000 households, prevalence estimates were approximately 3% to 6% of US women aged 18 years or over who met these IC symptom criteria for IC/PBS.

Nickel and the Interstitial Cystitis Deep Phenotyping Research Group[76] examined the phenotypic associations between IC/PBS and irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and other associated medical conditions in a case-controlled study. Two hundred five female patients with IC/PBS and 117 age-matched controls underwent a phenotyping battery that included demographics, duration of IC diagnosis and symptoms, self-reported history of associated conditions, 6 validated symptom questionnaires, 4 suffering and coping questionnaires, and 3 questionnaires examining quality of life, sexual functioning, and social support. This study showed that IC/PBS patients, compared with age-matched subjects with no IC/PBS diagnosis, reported experiencing greater pain and lower quality of life; this can only be categorized as dismal. It appears as though stress, depression, anxiety, and maladaptive cognitive pain appraisals (eg, catastrophizing) are intimately related to increased IC/PBS symptoms and bother, general pain, and poor quality of life. Furthermore, irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome are significantly more prevalent in IC/PBS patients than in controls, and result in significant impact on pain, quality of life, and important psychosocial parameters. There appears to be a phenotypic progression over time from an organ centric to a regional and finally to systematic pain syndrome, with progression of symptom severity and deterioration of some cognitive and psychosocial parameters associated with IC/PBS.

Kuo and Chancellor[77] undertook a prospective, randomized study in which 67 patients with IC who failed conventional treatments were randomized to receive either 200 (n = 15) or 100 U (n = 29) of suburothelial botulinum toxin A (BoNT-A) followed by a cystoscopic hydrodistention 2 weeks later. The control group (n = 23) received the identical hydrodistention procedure without the BOTOX injection. The results suggested that intravesical injections of BoNT-A followed by hydrodistention provide significantly better clinical results compared with hydrodistention alone in patients with IC.

Pinto and colleagues[78] studied 17 patients with bladder pain syndrome before and after treatment of bladder trigone alone injections of 100 U BoNT-A. This study demonstrated that intratrigonal injection of BoNT-A in patients with refractory PBS is safe and might be an effective alternative treatment. Ueda and colleagues[79] assessed 50 IC patients to determine the efficacy of urine alkalization in reducing symptoms. The results suggested that urine alkalization using citrates could be effective for reducing symptoms, especially pain at voiding and sleep disturbance in patients with IC.

Reeves and colleagues[80] conducted a retrospective case review on 15 patients with IC/PBS who failed to respond to therapy and who were referred for acupuncture. The investigators reported that acupuncture was successful in 100% of patients in terms of improving symptoms and 86% developed an improvement in quality of life. These results were particularly impressive in a cohort of patients who failed cystodistention and both oral and intravesical therapy.

Tsuchida and colleagues[81] conducted a preliminary study on 2 types of Chinese herbal medicine containing aconitine in 10 IC patients resistant to the usual therapy. In this pilot study, the investigators noted that these Chinese herbal medications resulted in a statistically significant decrease in pain. There was, however, some discussion of possible toxicity associated with this particular botanical preparation.

In a late-breaking plenary research presentation, on behalf of the ICCRN, Hanno[82] presented the recent NIH-sponsored trial evaluating the effect of amitriptyline on symptoms in newly diagnosed patients with IC/PBS. Although amitriptyline is the most commonly prescribed medication for the treatment of IC/PBS, data supporting its use are sparse. Using a multicenter, controlled trial, patients with IC/PBS were randomized to receive education and behavioral modifications plus either oral amitriptyline or matching placebo for 6 weeks. Although there was no statistical difference in overall primary efficacy endpoint (intent to treat, n = 271) between the amitriptyline and placebo arms (a response rate of 54% and

45%, respectively; $P = .12$), a posthoc comparison among participants (n = 207) that obtained a high dose (≥ 50 mg) of study drug, the response rate was 66% for the amitriptyline arm compared with 47% for the placebo arm ($P = .01$). The researchers concluded that although in the overall population amitriptyline combined with education/behavioral modification was not significantly different from education/behavioral modification plus placebo, there appeared to be some patients who did experience significant improvement with the active therapy.

CP/CPPS

Shoskes and colleagues[83] recognized that CP/CPPS is a heterogeneous syndrome with variable treatment responses. The investigators proposed a clinical phenotype system (UPOINT) to classify patients with UCPPS to help understand the etiology and guide therapy. Ninety men with CP/CPPS were classified in each domain of the UPOINT system using data from the first clinical visit as urinary (voiding symptoms), psychosocial (depression, catastrophizing, etc), organ specific (prostate tenderness, inflammation, etc), infection (localized uropathogens in prostate fluid without UTI, etc), neurologic/systemic (pain outside pelvis, fibromyalgia, irritable bowel syndrome), and tenderness (pelvic floor spasm or trigger points). Percentage of patients positive for each domain was U-52%, P-34%, O-61%, I-16%, *N*-37%, and T-53%. Twenty-two percent had only 1 domain and there was a significant stepwise increase in total CPSI severity scores as number of positive domains increased. Symptom duration, but not age, was associated with more positive domains. Only the psychosocial and neurologic domains influenced quality of life, whereas domains outside the prostate produced the most significant impact on symptoms. Because each domain has specific targeted therapies, the authors propose that multimodal therapy may best be guided by the UPOINT phenotype.

Tripp and colleagues[84] compared the prevalence and impact of CP/CPPS symptoms in white Canadian and black African Kenyan adolescents to determine if CP/CPPS is actually a white, middle-aged, western phenomenon as has been suggested by many authors. The investigators reported that the prevalence of at least mild CP-like symptoms was 6.8% and 9% for Canadian and African men, respectively, and that the symptoms had a significant impact on quality of life in both groups. CP/CPPS symptoms do not appear to be related to age, ethnicity, or culture.

Yoo and colleagues[85] analyzed the efficacy of a portable transrectal thermal therapeutic device for CP/CPPS. One hundred twenty patients were randomized into a medical therapy group, a device therapy group, and a combination medical/device therapy group. Although there appeared to be no significant difference between the group treated with standard medical therapy and those treated with the transrectal thermal device, the combination of medical and device therapy appeared to be statistically better than medical therapy alone. However, discussion centered on the less-than-impressive temperatures achieved with this device.

Oh and colleagues[86] evaluated the application of pelvic floor radiofrequency therapy in 30 men with CP/CPPS. Twenty men were randomized to the active treatment group, and 10 were randomized to a placebo treatment group. The within-group analysis showed that patients receiving active therapy had a significant response compared with baseline compared with placebo, but no intergroup analysis was presented. The use of pelvic floor radiofrequency therapy may help some patients with evidence of pelvic floor muscular dysfunction and this therapeutic option should be further explored.

Zeng and colleagues[87] reported on 40 men with category IIIB CP/CPPS randomized to extracorporeal shock wave therapy compared with a control group (n = 20) who underwent a sham procedure. Both treatments experienced a decrease in CPSI score; however, the investigators report that after the 4-week follow-up, the actively treated group had perceptible clinical improvement compared with the sham-treated group. Further studies are warranted to determine the reproducibility of these effects in a larger sample size.

Dimitrakov and colleagues[88] evaluated the efficacy and safety of memantine, a noncompetitive *N*-methyl-D-aspartate (NMDA)–receptor blocker in the alleviation of CPPS symptoms in 170 men randomly assigned to receive memantine or placebo for 1 year. At 6 months (in the 1-year trial), patients in the active treatment group reported significant improvement in pain, global symptoms, and quality of life compared with patients in the placebo group. This particular therapy has solid theoretical basis—the possibility of clinically phenotyping patients to best select directed therapy. This particular approach to the treatment of CP/CPPS should be carefully reviewed, and if the results are confirmed, the treatment should be further studied in larger cohorts in a well-designed, rigorously carried out, multicenter clinical trial.

Pontari[89] reported for his colleagues from the Chronic Prostatitis Collaborative Research Network on the NIH randomized, placebo-controlled, multicenter trial of pregabalin for the treatment of men with CP/CPPS. Men with CP/CPPS were randomly assigned

to either pregabalin or matching placebo in a 2:1 ratio, respectively, for 6 weeks. The daily dose was increased at 2-week intervals beginning with 150 mg to 300 mg and finally to 600 mg. Among the 218 men assigned to pregabalin, 47.2% reported at least a 6-point decrease in total CPSI score at 6 weeks compared with 35.8% of 106 men assigned to placebo ($P = .072$). An analysis of important secondary endpoints including CPSI total score, the 3 CPSI subscores (pain, urinary, and quality of life), and the global response assessment (GRA) all showed statistically significant improvement in the active treatment group versus the placebo group (eg, 31% and 19%, respectively, for the GRA; $P = .023$). Although the authors reported that the primary endpoint showed no superiority of pregabalin therapy to placebo, the impressive differences in secondary endpoints suggested that pregabalin may prove effective in some men with longstanding CP/CPPS.

Summary

It appears that the evolution now occurring in our understanding and management of patients diagnosed with UCPPS is the awareness that patients are unique, with varying clinical phenotypes and that targeted therapy will likely be the key to future success in treating IC/PBS and CP/CPPS.

[J. Curtis Nickel, MD, FRCSC]

Genitourinary Oncology

As expected, the 2009 AUA Annual Meeting was an exciting time for the field of genitourinary oncology. The major highlights presented at the meeting included major advances in immunotherapy for prostate cancer from Dendreon Corporation (Seattle, WA), positive results for chemoprevention of prostate cancer from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, and further analyses of the role of prostate cancer screening from the PLCO study. However, there were many interesting presentations in other areas of genitourinary oncology, such as renal cell carcinoma and adrenal tumors that received less attention, but also may prove important to the care of cancer patients.

Renal Cell Carcinoma

The field of kidney cancer continues to be very active, with new studies and new data for the treatment of both early stage and advanced disease. The introduction of several new targeted agents in the management of metastatic disease has provided the oncology community with agents that, in most patients, can achieve clinical benefits not previously observed in the immunotherapy era. These drugs have also been applied to the presurgical setting with several initial series demonstrating responses in the primary tumor. Additionally, increasing reports have shown the feasibility of the observation strategy for small renal masses now with intermediate-term follow-up. Also exciting are the continued advances in the application of minimally invasive techniques, such as robotic surgery for the management of small renal masses.

Introduced at the meeting for the first time were new kidney cancer recommendations by the AUA Renal Mass Panel entitled "Guideline for the Management of the Clinical Stage T1 Mass." Based on review of the available literature, all relevant articles were selected for various meta-analyses of the different treatment modalities. The consensus of the panel was that partial nephrectomy is now the standard of care for T1a tumors and should be considered whenever technically feasible. The laparoscopic and open approaches are both considered applicable; however, because increased rates of complications such as hemorrhage and urinary fistula are increased with the minimally invasive approach, this should be mentioned when discussing the options with patients. Also recommended is the discussion of ablative techniques and surveillance options when counseling patients on management options. However, this discussion should also include mention that risk of local recurrence appears higher in patients undergoing ablation rather than excision. Additionally, physicians should discuss the risk of metastasis during observation and the potential for interval growth during this period resulting in a missed opportunity for nephron-sparing surgery. For patients with T1b tumors (> 4 cm), radical nephrectomy still remains the standard of care for healthy patients; however, partial nephrectomy should be discussed as a potential option if surgically feasible.

Although the AUA renal mass panel has come out with its recommendations favoring nephron-sparing surgery, it was interesting to see that possible discrepancies exist in the utilization of partial nephrectomy. Two abstracts presented focused on the use of partial nephrectomy from the analysis of claims-based data from different resources. Johnson and colleagues[90] assessed the trends in utilization of both partial nephrectomy and laparoscopy between teaching and nonteaching hospitals during 2 separate years (2004 and 2006). The initial analysis demonstrated that at nonteaching centers, patients were almost twice as likely to have a radical nephrectomy and nearly half as likely to have it done laparoscopically. These trends between both hospital types appeared to become less severe in 2006, potentially reflecting the diffusion of surgical innovation. Kutikov and colleagues[91] found in their analysis that Medicare beneficiaries were

24% less likely to receive a partial nephrectomy compared with patients covered by private insurance. The reasons for this remain unclear, but warrant further investigation.

Observation of small renal masses has been a new concept in the field of renal cell carcinoma the past few years, as several retrospective series have been presented demonstrating excellent cancer specific survival in patients with small renal tumors.[92] This option has been a preferred management strategy for mainly elderly patients or those with comorbidities. Jewitt and colleagues[93] presented the results of a prospective clinical trial assessing the feasibility of observation. Patients were offered a biopsy at the start of the trial and had serial imaging to determine interval growth or development of distant disease. At a short follow-up of 15 months, only 2 patients had progression to metastatic disease. Tumors were demonstrated to have median growth rate of only 0.35 mm/year. The trials definition of local progression was size larger than 4 cm or doubling volume in less than 12 months; only 7 patients met these criteria during the study period. With longer follow-up, this prospective study will provide us with more information on the risk of local extension and the development of metastatic disease with observational strategies.

A fraction of small renal masses may represent aggressive cancers and observation of these lesions may lead to disease progression. Identification of biomarkers that can predict the malignant potential of these small renal masses can potentially select patients for more aggressive therapies. La Rochelle and colleagues[94] assessed the relationship of chromosome 9p deletions to clinicopathologic variables and patient outcome for small ($<$ 4 cm) clear cell renal tumors undergoing nephrectomy. Cytogenetics and fluorescence in situ hybridization assessed 9p loss, which was found in 10% of tumors. Recurrence-free survival (RFS) was significantly worse for those patients with loss of 9p (43% vs 7%; $P = .001$). In the multivariate model, this unique cytogenetic change was an independent predictor of worse RFS. The expanding role of percutaneous biopsy of small renal masses may not only allow the determination of malignancy, but eventually be used to risk-stratify patients and select for appropriate treatment.

As partial nephrectomy has become the gold standard for T1a tumors, recent studies have demonstrated that nephron-sparing for larger tumors is feasible and has a similar oncologic outcome compared to radical nephrectomy.[95,96] The new AUA guidelines recommend discussion of partial nephrectomy for clinical T1b tumors. Several abstracts confirmed that nephron-sparing surgery for these tumors provides similar cancer specific outcomes and may in fact yield an improved overall survival advantage. Thompson and colleagues[97] reported the outcomes of over 1100 patients undergoing either partial or radical nephrectomy for tumors 4 to 7 cm. Patients undergoing partial nephrectomy more frequently had solitary kidneys or renal insufficiency. Overall survival between groups appeared similar despite choice of surgery. Interestingly, those patients undergoing radical nephrectomy were more than twice as likely to die from their disease. When controlling for other variables, this association was also observed but failed to reach significance. Weight and colleagues[98] presented a similar study; however, this study focused on patients with clinical T1b tumors that were candidates for an "elective" nephron-sparing surgery. In this analysis, an overall survival benefit was observed for partial nephrectomy and this association appeared to be influenced by the maintenance of renal function. Thus, as included in the new AUA guidelines, patients with tumors 4 to 7 cm who are candidates for partial nephrectomy should be counseled on the similar oncologic efficacy and the potential benefits of preserved renal function with nephron-sparing surgery.

The genetic alterations associated with clear cell renal cell carcinoma and the von Hippel-Lindau (VHL) pathways continue to be elucidated as we find new agents to exploit this pathway. Currently it is believed that alterations in VHL gene occur in 80% to 90% of patients with sporadic clear cell renal cell carcinoma.[99] The molecular mechanisms responsible for carcinogenesis with VHL alterations are influenced by the dysregulation and overexpression of hypoxia inducible factor; however, many other pathways interact with the VHL protein and may play a role in the development of malignancy. If we can better characterize the cellular changes associated with loss of the VHL protein, we can continue to develop new therapeutic agents. Rettig and colleagues[100] analyzed important downstream events that result from the loss of the VHL gene in paired isogenic cell lines differing in the expression of VHL due to an inhibitory viral vector. VHL-deficient cell lines demonstrated different morphology and had more invasive properties. Epithelial to mesenchymal transformation appeared to occur with loss of VHL as specific proteins involved in this process such as N- and E-cadherin and vimentin differed between cell lines. VHL loss leads to the activation of key inflammatory mediator nuclear factor κB (NFκB). This interesting study demonstrated that inhibition of NFκB could reverse the epithelial-mesenchymal transition changes associated with VHL

loss. As new agents have been developed that can potentially target this pathway, this study encourages their use in patients with sporadic clear cell renal cell cardinoma.

Adrenal Diseases

Several interesting abstracts were presented on the management of adrenal disorders. Some of these included the role of laparoscopy in the management of adrenal cortical carcinoma and the clinical characteristics to distinguish benign and malignant pheochromocytomas. Additionally, several abstracts dealt with the role of partial adrenalectomy and the preservation of hormone function after use in a solitary adrenal gland.

Brix and colleagues[101] presented an analysis of the German Adrenal Cortical Carcinoma Registry. Several prior reports have raised concern over laparoscopic adrenalectomy for large adrenal tumors suspicious for adrenal cortical carcinoma. Concerns over invasion into adjacent organs, carcinomatosis, or positive surgical margins have prompted most surgeons to use an open approach for resection. For this analysis, 135 cases of stage I to III tumors 10 cm or smaller were reviewed. A total of 27 cases underwent laparoscopic adrenalectomy (the largest series to date). These cases were matched by clinicopathologic characteristics to patients undergoing open adrenalectomy. At a median follow-up of 3 years, there was no difference in the time to recurrence or overall survival for either approach. However, not surprisingly, there was need for open conversion in 11 of 27 (41%) cases. These findings support that a laparoscopic approach may be feasible in select patients; however, patients and surgeons must be willing to accept a high rate of conversion. As this is a very aggressive disease, a good cancer operation should not be compromised for a shorter hospital stay.

Patients with pheochromocytomas require long-term surveillance postoperatively as no pathologic characteristics can distinguish benign and malignant pheochromocytomas. Park and colleagues[102] reviewed 152 cases and found 17 (11.1%) that were determined to be malignant pheochromocytomas. Clinicopathologic and laboratory characteristics from these cases were compared with benign tumors. Patient characteristics, including age, gender, and symptoms, were no different between benign and malignant pheochromocytomas. Tumors with malignant potential were significantly larger (11.1 vs 6.1 cm). Although 24-hour urinary catecholamines were uniformly elevated, patients with malignant pheochromocytomas had decreased and only mildly elevated vanillylmandelic acid (VMA) epinephrine. These results can potentially allow risk-stratified surveillance with patients with large tumors with low VMA levels having closer follow-up. Additionally, there is no consensus on staging for pheochromocytoma preoperatively. As malignant pheochromocytomas can spread to the chest, lungs, liver, bone, and lymph nodes, during the initial workup a chest computed tomography or a bone scan should be considered in a patient with high risk for metastatic disease.

Two studies out of the National Cancer Institute assess the partial adrenalectomy for small adrenal masses. The study by Kaye and colleagues[103] assesses the current literature on the use of partial adrenalectomy. A total of 24 papers describe the use of partial adrenalectomy for small adrenal masses. Partial adrenalectomy can be safely performed for either hyperfunctional lesions or benign adenomas. These small adrenal masses (mean size, 2.7 cm) were frequently handled laparoscopically. The mean follow-up for these series was fairly long at 55 months, with a low overall recurrence rate (6.3%). The second study reported by Sanford and colleagues[104] reported the functional outcomes after partial adrenalectomy for patients with a pheochromocytoma in a solitary adrenal gland. A total of 19 patients were evaluated, 17 of whom had hereditary syndromes such as VHL, multiple endocrine neoplasia II, or neurofibromatosis I. The functional outcomes for these patients were excellent, with 73.6% (14/29) of patients ultimately having enough residual function from their remaining adrenal gland to remain free of hormonal supplementation. With long-term steroid supplementation having significant morbidity, it appears that adrenal surgery may be moving to a less radical approach favoring partial adrenalectomy and minimally invasive surgery when feasible.

Conclusions

The 2009 AUA meeting was an excellent forum for researchers all over the world to present advances in genitourinary oncology and to discuss where our field is heading. It is hoped that this energy can be carried over to new projects to make the 2010 meeting even more productive.

[B. Shuch, MD, F. Pouliot, MD, Arie S. Belldegrun, MD, FACS]

Pediatric Urology

Trauma

Voelzke and colleagues[105] presented their 29-year experience on delayed repair for pediatric urethral stricture following urethral trauma. They presented 27 boys younger than 18 years of age (mean age, 15 years); there were 19 posterior urethral strictures and 8 anterior (8 bulbar/straddle injury). All posterior urethral strictures were treated with an initial suprapubic tube diversion at the time of injury. All of these patients had other injuries,

whereas only 1 of the patients with an anterior urethral injury had an associated injury. The mean follow-up was 1.76 years (median, 0.85 years). The 2 main surgical techniques employed were anastomotic (23 patients) or buccal mucosal onlay graft (3 patients). One patient with a mild urethral stricture required only urethral dilation. A single-stage procedure was performed. A partial pubectomy was required in 5 of 18 patients with posterior urethral strictures.

The outcomes for these urethroplasties revealed an overall success rate for anterior urethral stricture of 88.9% and for posterior strictures of 89.5%. There was 1 anastomotic failure in the anterior stricture group occurring after 1 year, whereas 2 anastomotic failures in the posterior group occurred earlier, at 4.5 and 9 months. All 3 of these patients responded to an internal urethrotomy, although 1 failed anterior repair and 1 of the 2 failed posterior repairs required 2 internal urethrotomies. Repeat urethroplasty was not required in any patient. All patients had satisfactory continence.

Urinary Tract Infection

Nguyen and colleagues[106] performed a multi-institutional study of the antibacterial activity of trimethoprim and whether it is increased by the addition of sulfamethiazole. This is an important question because this medication is commonly used to treat urinary tract infections in children, and 3% of patients developed an allergic reaction to sulfamethiazole with serious consequences such as hepatic failure, Stevens Johnson syndrome, and anaphylactic shock. Allergic reaction to trimethoprim is less common. These investigators examined 565 children with a documented urinary tract infection and prospectively determined whether there was any regional difference between trimethoprim and sulfamethiazole sensitivities. Using the disc diffusion method, in vitro sensitivity of bacteria isolates to sulfamethiazole and trimethoprim and combination sulfamethiazole/trimethoprim were determined. No statistical difference was found between trimethoprim and sulfamethiazole and sulfamethiazole/trimethoprim. No regional differences were found within this study. These authors recommended that trimethoprim can be used as an alternative to the trimethoprim/sulfamethiazole without compromising treatment efficacy.

Long-Term Follow-Up of Enteric Urologic Surgery

Granberg and colleagues[107] from the Mayo Clinic examined 3 different questions regarding outcomes in patients undergoing reconstructive surgery using various bowel segments. The first question examined vitamin B_{12} deficiency in those patients with ileocecocystoplasty, Indiana pouch, or ileal conduit. One hundred sixty-nine patients were included in the study. During a median follow-up of 14 years, 9% (7/80) of patients with an ileocecocystoplasty developed vitamin B_{12} deficiency. After a median follow-up of 14 years (mean, 8-28 years), 4.5% (2/45) of patients with an Indiana pouch developed vitamin B_{12} deficiency. During a median follow-up of 30 years, 7% (3/44) of patients with an ileal conduit developed vitamin B_{12} deficiency.

The researchers also examined renal preservation in these same groups.[108] Of the patients undergoing ileocecocystoplasty with a mean follow-up of 14 years, 12 patients had either renal insufficiency (7) or end-stage renal disease (5). Eight (67%) of the patients with renal insufficiency or end-stage renal disease (ESRD) had a history of noncompliance with intermittent catheterization. Forty percent (32 patients) developed renal scarring or underwent nephrectomy due to complications. In patients with Indiana pouch urinary diversion with a mean follow-up of 14 years, 3 patients (7%) developed renal insufficiency (2) or insistent renal disease (1). Two of these patients had a history of noncompliance with intermittent catheterization. Renal scarring or a loss of a kidney occurred in 11 (24%) of these patients. In the ileal conduit group of 44 patients followed for a mean of 30 years, 11 patients (24%) developed either renal insufficiency (5) or ESRD (6). The statistical analysis showed that patients with either an ileocecocystoplasty or Indiana pouch urinary diversion had better renal preservations than those with an ileal conduit ($P < .01$). The authors conclude that all forms of enteric urological reconstruction place patients at risk for long-term renal insufficiency or ESRD. Those patients who are on clean intermittent catheterization must be compliant because noncompliance appears to be a significant factor in the development of renal impairment.

Higuchi and Husmann[109] reported on 50 patients who had undergone enterocystoplasty 10 years ago or longer. Forty patients had ileal augmentation and 10 had colonic cystoplasty. They performed 250 surveillance endoscopies with only 1 suspicious lesion removed. The pathology on the lesion was an adenomatous polyp and has not reoccurred. Of the 250 urine cytologies examined, 10% of the specimens were suspicious for malignancy. Endoscopy and computed tomography urogram failed to identify any malignancy. Because there was a low event rate and high cost of surveillance, these protocols were discontinued after 5 years. These investigators recommend

routine interval medical history, radiographic studies, and urinalysis. Endoscopic evaluations and cytologies would be indicated for a history of more than 4 symptomatic urinary tract infections per year, bladder or pelvic pain, gross hematuria or persistent microscopic hematuria, or any abnormality found on radiographic studies. This new protocol has been in place for 8 years (range, 5-7 years) and no patients have developed bladder tumors. These investigators present a cost effective, practical approach to surveillance in this complex group of patients.

Vesicoureteral Reflux

Kaye and colleagues[110] have noted that the criteria for success following endoscopic therapy for vesicoureteral reflux (VUR) vary among investigators. Successfully treated patients may develop recurrent reflux and initial failures may require no additional treatment. These authors propose a new definition of outcomes based upon radiographic and long-term clinical follow-up. They reviewed all of their patients with primary grade 1 to 4 VUR who had undergone endoscopic therapy with 1 year or longer follow-up. These patients underwent a postoperative voiding cystourethrogram (VCUG) in a mean of 3 months and all recurrent urinary tract infections prompted a repeat VCUG. Radiographic cure (success) was defined as no VUR on postoperative VCUG and clinical cure (success) was defined as no febrile urinary tract infections during follow-up. They report their experience between 2004 and 2008. Of 336 patients (296 girls and 40 boys; mean age, 4 years) treated with dextranomer and hyaluronic acid via a double hydrodistention-implantation technique, initial radiographic success was 90% (294/336). Pyelonephritis occurred in 19 and of those 19 patients reimaged, 12 had recurrent VUR (4% of cures). Of the radiographic cures, 1.7% had open surgery, whereas 17% of the radiographic failures were observed with no additional treatment. Overall, 93% (314/336) of all patients treated were clinical successes—free of febrile urinary tract infection. A febrile urinary tract infection occurred in 3% (10/294). When success is defined as radiographic cure and clinical absence of febrile urinary tract infection, success was 82% (275/336). When it is defined radiographically alone, success was 84% (282/336). If success is defined clinically alone, then success was 93% (314/336). Of all the patients treated, 6.5% (19/336) underwent open surgery. If success is defined as no additional procedures, then success was 94% (317/336). Ideally, successful procedure eliminates reflux and postoperative febrile infections. This breakdown in terminology may be useful in counseling families who are considering endoscopic treatment for VUR. ■

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